Efficacy and Safety of Coadministration of Ezetimibe and Simvastatin in African-American Patients with Primary Hypercholesterolemia

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Financial support: This study was sponsored by Merck/Schering Plough Pharmaceuticals, New Wales, PA.

The purpose of this study was to examine the efficacy and safety of ezetimibe (EZE) coadministered with simvastatin (SIMVA) in a large cohort of African Americans with primary hypercholesterolemia. In a multicenter, randomized, double-blind study, patients were considered eligible for enrollment if after a washout/placebo run-in period, low-density-lipoprotein (LDL) cholesterol level was ≥145 and ≤250 mg/dl and triglyceride level was ≤350 mg/dl. Eligible patients were randomized to SIMVA 20 mg coadministered with either EZE 10 mg (n=124) or placebo (n=123) for 12 weeks. At study endpoint, EZE/SIMVA 10/20 mg resulted in a significant mean percent reduction in LDL cholesterol from baseline of 45.6% compared with 28.3% for SIMVA 20 mg alone ($p \leq 0.01$). There were significantly greater mean reductions in total cholesterol (33% vs. 21%), triglycerides (median 22% vs. 15%), nonhigh-density-lipoprotein (non-HDL) cholesterol (42% vs. 26%), and apolipoprotein B (38% vs. 25%) with EZE/SIMVA 10/20 mg compared with SIMVA 20 mg alone, respectively ($p \leq 0.01$). There was no difference in HDL cholesterol between the EZE/SIMVA 10/20-mg and SIMVA 20-mg alone groups (+1% vs. +2%, respectively). Coadministration of EZE/SIMVA 10/20 mg demonstrated a safety profile similar to that of SIMVA 20 mg. In conclusion, EZE/SIMVA 10/20 mg provided significantly greater improvement in atherogenic lipid profiles and was well tolerated compared with SIMVA 20-mg monotherapy in a large cohort of African Americans with primary hypercholesterolemia.

Key words: cholesterol absorption inhibitor ■ statin ■ race/ethnicity ■ LDL cholesterol

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Mortality from coronary heart disease (CHD) is the highest in African Americans compared with other ethnic groups in the United States.[1,2] African Americans also tend to have a greater prevalence of multiple CHD risk factors, including type-2 diabetes and hypertension.[3] This clustering of CHD risk factors may increase the proportion of African Americans categorized as high risk or very high risk according to NCEP ATP III guidelines.[2,4] As recommended by NCEP ATP III guidelines, more intensive lipid-lowering therapies should be implemented for patients at high risk for CHD.[2]

Statins (HMG CoA reductase inhibitors) are the most effective lipid-lowering medications available and act by inhibiting hepatic cholesterol synthesis.[5] Ezetimibe (EZE) is a cholesterol absorption inhibitor, which lowers lipid levels by preventing the intestinal absorption of dietary and biliary cholesterol without affecting the absorption of triglycerides or fat-soluble vitamins.[6,7] When EZE was coadministered with a statin, there was a significant incremental reduction in low-density-lipoprotein (LDL)-cholesterol levels compared with statin monotherapy.[8-11] This result was generally consistent across all subgroups examined, except race. In a pooled analysis of the four large factorial trials referenced above, the coadministration of EZE with a statin reduced LDL-cholesterol levels by 14.6% in Caucasians compared with 6.6% for non-Caucasians after 12 weeks of treatment.[12] African Americans comprised 5.3% (n=126) of this pooled cohort.[12] A subgroup analysis by different races suggested that this finding may be due to a diminished efficacy of coadministration therapy on percent reductions in LDL-cholesterol levels for African Americans compared with other non-Caucasians (+1.3% vs. -12.0%) (data on file Merck/Schering Plough Pharmaceuticals).

Due to the limited enrollment of African-American subjects in the EZE and statin coadministration trials and inconsistent efficacy results in this cohort,

the purpose of this study was to examine the efficacy and safety of the coadministration of EZE with SIMVA compared with that of SIMVA monotherapy in a large cohort of African Americans with primary hypercholesterolemia.

METHODS

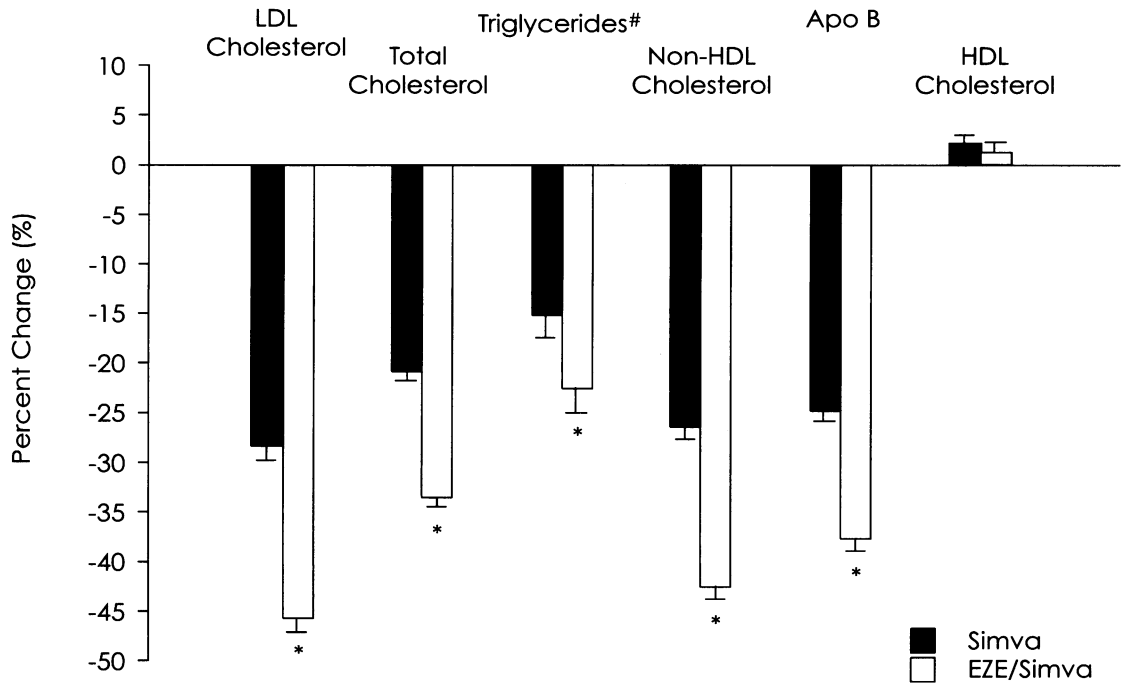
Patients

African-American and black men and women (age ≥18 years) were considered eligible for enrollment in this study if they had primary hypercholesterolemia (defined as LDL-cholesterol level ≥145 and ≤250 mg/dl after a washout placebo run-in period). Racial designation of African-American or black was made by the participant. Exclusion criteria included a cardiovascular event within three months of study enrollment; congestive heart failure (NYHA class 3 or 4); uncontrolled cardiac arrhythmias; severe aortic stenosis; obstructive cardiomyopathy; uncontrolled hypertension (systolic blood pressure >160 and/or diastolic blood pressure >100 mmHg); poorly controlled type-1 or type-2 diabetes (HbA_{1c} >9.0%); active or chronic hepatobiliary disease; or impaired renal function (plasma creatinine ≥2.0 mg/dl). Patients were not permitted to continue taking lipid-lowering therapies and on medications, which were potent inhibitors of CYP 3A4 during the study. All prospective patients provided a signed informed consent.

Study Design

The efficacy and tolerability of the coadministration of EZE 10 mg and SIMVA 20 mg compared with SIMVA 20 mg were evaluated in this 12-week, multicenter, randomized, double-blind, placebo-controlled study. After the completion of a 6–8-week washout period, placebo pills were administered to match EZE and SIMVA during a four-week, single-blind, lead-in period. Patients were also instructed to follow an NCEP Step-1 diet throughout the screening and treatment periods. If the LDL-cholesterol level was ≥145 and ≤250 mg/dl, triglycerides were ≤350 mg/dl, and hepatic transaminases and creatine phosphokinase (CPK) were ≤2 times the upper limit of normal after this period, eligible patients were randomized to SIMVA 20 mg coadministered with either EZE 10 mg or placebo in a 1:1 ratio using a computer-generated, random allocation schedule, and randomization was stratified by gender. The study was conducted in accordance with Good Clinical Research Practice. The protocol was approved by the institutional review board or ethics committee of each study center.

Figure 1. Mean percent change (standard error) in various lipid parameters from baseline after treatment with coadministered ezetimibe 10 mg and simvastatin 20 mg (EZE/SIMVA) or simvastatin 20 mg (SIMVA) monotherapy



Values for triglycerides are median percent change (SE); * p≤0.01 for the comparison between treatment groups

Study Variables

The primary efficacy variable was the percent reduction in LDL-cholesterol level from baseline to study endpoint. The endpoint value was defined as the last postbaseline measurement during the 12-week, double-blind treatment period. Subgroup analyses were performed on the percent reduction in LDL-cholesterol levels for the following groups: age (<65, ≥65 years), gender, body mass index (BMI <30 or ≥30 kg/m^2), hypertension status, diabetes status, established CHD status, number of cardiovascular risk factors (<2 or ≥2) and baseline LDL-cholesterol level (<160, ≥160 mg/dl). Secondary efficacy variables were the percent change from baseline to study endpoint in total cholesterol, high-density-lipoprotein cholesterol (HDL cholesterol), triglycerides, non-HDL cholesterol, apolipoprotein (apo) B and high-sensitivity C-reactive protein (hs-CRP).

Safety and tolerability were assessed by monitoring adverse events, laboratory parameters and vital signs throughout the trial. Adverse events were reported by the patient or were observed by the investigator. While blinded to the treatment allocation, the investigators also rated the adverse events in terms of the intensity (mild, moderate or severe), seriousness (e.g., death, cancer, life-threatening events, disability/incapacitation and/or prolonged hospitalization) and the relationship to study medication (e.g., definitely, probably, possibly or not related). Laboratory safety parameters, including aspartate aminotransferase (AST), alanine aminotransferase (ALT) and CPK were monitored during the study. Parameters were assessed according to the standard predefined limits of change and change from baseline. Laboratory adverse events were defined as serious and treatment was discontinued if any of the following parameters were met: consecutive increase in AST/ALT levels ≥3 times the upper limit of normal, consecutive increase in CPK levels ≥5 times the upper limit of normal with muscle symptoms, and consecutive elevations in CPK levels ≥10 times the upper limit of normal. Adherence to treatment was assessed by tablet count.

Blood Collection and Assay Procedures

Blood samples were collected after a 12-hour fast. Lipid profiles and nonlipid parameters were measured in plasma at various time points throughout the study. These variables included LDL cholesterol, triglycerides, HDL cholesterol, total cholesterol, non-HDL cholesterol, apo B and hs-CRP. Total cholesterol and triglyceride levels were determined enzymatically. LDL-cholesterol level was estimated using the Friedewald calculation.[13] HDL-cholesterol level was quantified enzymatically after the selective removal of apo B-containing lipoproteins by heparin and manganese chloride precipitation. Non-HDL-cholesterol level was calculated by subtracting the HDL-cholesterol level from total cholesterol level. Apo B levels were determined by fixed-rate nephelometry. Hs-CRP level was measured by high-sensitivity immunonephelometry (Dade Behring Inc., Deerfield, IL). All clinical laboratory analyses were performed at the central laboratory (Medical Research Laboratory, Highland Heights, KY).

Table 1. Baseline demographics and characteristics in African-American patients prior to treatment with coadministered ezetimibe 10 mg and simvastatin 20 mg or simvastatin 20 mg monotherapy for 12 weeks

Variables*	Simvastatin 20 mg (N=123)	Ezetimibe/Simvastatin 10/20 mg (N=124)
Age (years)	53.7 ± 11.5	55.2 ± 11.6
Weight (kg)	87.9 ± 16.6	87.7 ± 18.1
BMI (kg/m^2)	31.0 ± 5.7	31.3 ± 5.9
Men, n (%)	47 (38)	48 (39)
Women, n (%)	76 (62)	76 (61)
Diabetes Mellitus, n (%)	20 (16)	26 (21)
CHD, n (%)	13 (11)	12 (10)
CV risk ≥2, n (%)	67 (54)	61 (49)
LDL cholesterol, mg/dl	174.7 ± 23.3	176.5 ± 23.2
Total cholesterol, mg/dl	253.3 ± 27.0	256.3 ± 26.8
HDL cholesterol, mg/dl	50.2 ± 13.4	53.2 ± 13.4
Triglycerides, mg/dl†	125.5 ± 58.6	124.5 ± 60.0
Non-HDL cholesterol, mg/dl	203.1 ± 27.4	203.4 ± 27.4
Apo B, mg/dl‡	153.0 ± 24.9	156.3 ± 24.9

* Data are presented as mean ± standard deviation (SD) or frequency (%) unless otherwise indicated; † Median ± SD for medians; ‡ n=116 for simvastatin group; n=121 for ezetimibe + simvastatin group

Statistical Analyses

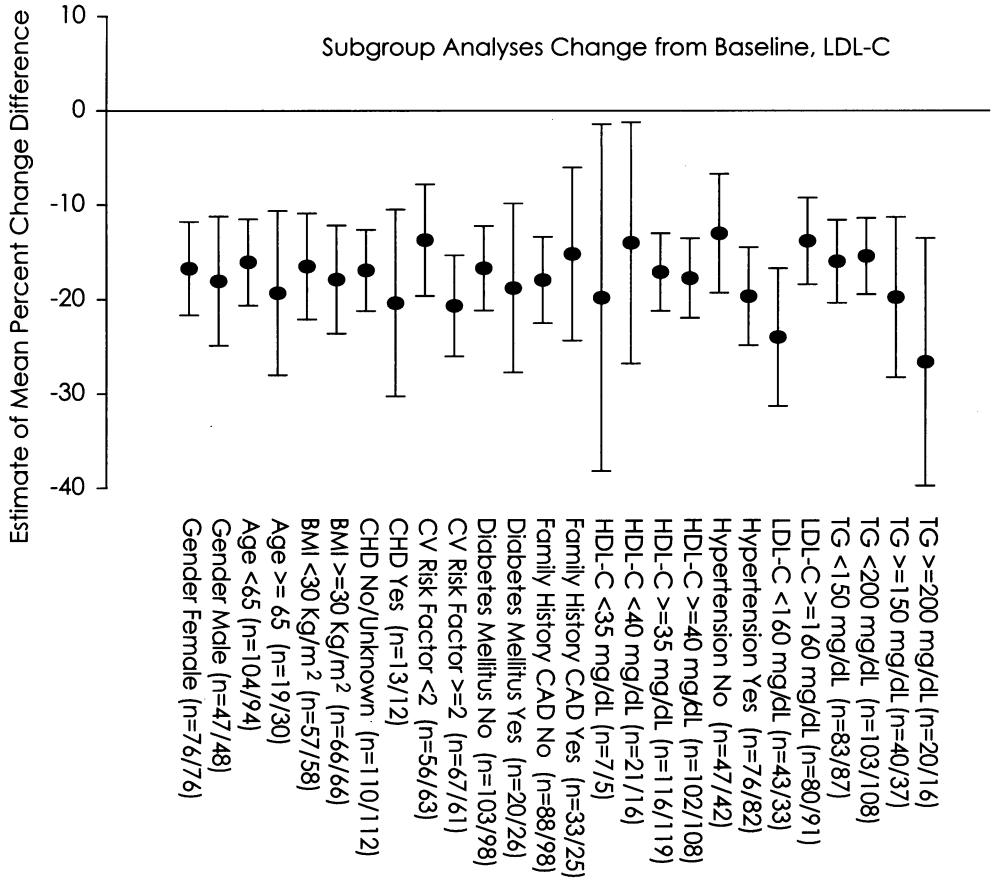
The efficacy analysis was based on a modified intention-to-treat approach, which included all patients who received at least one dose of randomized treatment, had a lipid measurement at baseline (for analysis of percent change), and who had at least one lipid measurement after the start of treatment. The percent change from baseline to study endpoint was assessed for LDL cholesterol (primary efficacy variable) and other lipid parameters by a two-way analysis of variance (ANOVA) with terms for treatment (EZE/SIMVA 10/20 mg and SIMVA 20 mg) and gender included in the model. For a sample size of 100 patients per treatment group, a difference between the cohorts of EZE/SIMVA 10/20 mg and SIMVA 20 mg of 7 percentage points in the mean percent reduction in LDL-cholesterol levels can be detected with 87% power, assuming a standard deviation of 16 and significance level of 0.05 (two-tailed). Percent LDL-cholesterol reduction at weeks 2, 4, 8 and 12 were evaluated in the same manner as the study endpoint analysis. Triglyceride levels were not normally distributed; thus, a comparable nonparametric test, a one-way ANOVA on the ranks, was used to evaluate treatment differences. The proportion of patients who achieve NCEP ATP III guidelines target LDL-cholesterol levels at the study endpoint regardless of their baseline LDL-cholesterol levels was tabulated for each treatment group.

The primary safety analyses compared the percentage of patients in the two treatment groups with any adverse events, treatment-related adverse events, serious adverse events and discontinuations due to adverse events using Fisher's exact test.

RESULTS

Of the 635 patients screened, 247 were randomized to receive either SIMVA 20 mg (n=123) or EZE/SIMVA 10/20 mg (n=124). Of the 388 patients excluded prior to randomization, most patients were excluded for one of the following: 304 did not meet protocol eligibility criteria (233/304 specifically did not meet lipid criteria), 46 withdrew consent prior to randomization and 20 were lost to follow-up. The treatment groups were generally well balanced for

Figure 2. Difference in mean percent change in LDL cholesterol (95% confidence intervals) between treatments (coadministered ezetimibe 10 mg and simvastatin 20 mg vs. simvastatin 20 mg monotherapy) for various subgroups of African-American patients



baseline demographics and lipid parameters (Table 1). For the randomized cohort, the mean age was approximately 55 years with a mean baseline LDL-cholesterol level of approximately 176 mg/dl. Women comprised >60% of this study cohort. The proportions of patients with CHD, type-2 diabetes or with ≥2 cardiovascular risk factors were also similar between the treatment groups.

At study endpoint, there was a significantly greater mean percent reduction in LDL-cholesterol levels from baseline in the EZE/SIMVA 10/20 mg group compared with the SIMVA 20-mg monotherapy group (between-group difference in least squares means=-17.2%, 95% CI: -21.2, -13.3; p≤0.01) (Figure 1). LDL-cholesterol levels were maximally reduced by week 2 with both treatments and were maintained throughout the duration of the study. The incremental reduction in LDL-cholesterol level was consistent across subgroups, which included age (<65, ≥65 years), gender, BMI <30 or ≥30 kg/m^2, hypertension status, diabetes status, established CHD status, number of cardiovascular risk factors (<2 or ≥2) and baseline LDL-cholesterol level (<160, ≥160 mg/dl) (Figure 2). Of the patients who were above their risk-specific LDL-cholesterol goal based on NCEP ATP III guidelines at baseline, a significantly greater proportion on EZE/SIMVA 10/20 mg achieved their target LDL-cholesterol level compared with those on SIMVA 20 mg (74% vs. 46%, respectively; p≤0.01).

At study endpoint, there were significantly greater reductions in the other lipid endpoints, including total cholesterol, triglycerides, non-HDL cholesterol and apo B with the coadministration of EZE/SIMVA 10/20 mg compared with SIMVA 20 mg at study endpoint (Figure 1). There was no difference in the change in HDL cholesterol between treatments. Baseline hs-CRP was similar between the EZE/SIMVA 10/20 mg (median ± standard deviation; 3.3 ± 5.3 mg/L) and SIMVA 20 mg (3.5 ± 4.6 mg/L) groups. Median hs-CRP was significantly reduced by 16.7%, with EZE/SIMVA 10/20 mg treatment and by 21.5% with SIMVA 20-mg treatment, but there was no significant difference between treatment groups.

Safety and Tolerability

Greater than 90% of randomized patients completed the 12-week treatment period. Ninety-five percent of patients had ≥75% compliance by pill count. The adverse event profiles were similar between the treatment groups (Table 2). Overall, the pattern in the reporting of adverse events (by body system and/or organ class) indicated no increased risk for African-American patients assigned to either treatment cohort. There was no treatment-related adverse event term or category that was particularly prevalent in either group. The rates of discontinuations for any reason and of adverse event-related discontinuations did not differ between treatment groups. There was one serious adverse event in the SIMVA 20-mg monotherapy group (sarcoidosis) and two serious adverse events in the EZE/SIMVA 10-/20-mg group (muscle abscess and CVA). These serious adverse events were not considered to be treatment-related by the investigators.

Table 2. Safety and tolerability in African-American patients treated with coadministered ezetimibe 10 mg and simvastatin 20 mg or simvastatin 20 mg monotherapy for 12 weeks

	Simvastatin 20 mg	Ezetimibe/Simvastatin 10/20 mg
Number of patients randomized	123	124
Number (%) of patients...		
With one or more adverse events	69 (56)	71 (57)
With treatment-related adverse events*	21 (17)	23 (19)
With serious adverse events	1 (1)	2 (2)
With serious treatment-related adverse events*	0 (0)	0 (0)
Discontinued due to any adverse events	4 (3)	3 (2)
Discontinued due to treatment-related adverse events*	1 (1)	2 (2)
Discontinued due to other reasons	10 (8)	7 (6)
Subject withdrew consent	4	1
Lost to follow-up	3	2
Protocol deviation	2	3
Administrative	1	1
Specific adverse events of interest		
ALT ≥3 times the upper limit of normal, consecutive	0	0
AST ≥3 times the upper limit of normal, consecutive	0	0
CK ≥10 times the upper limit of normal	1	0

* Determined by the investigator to be possibly, probably or definitely drug related

In the SIMVA 20-mg group, there was one case of CPK ≥10 times the upper limit of normal without associated muscle symptoms (Table 2). This patient reported participation in vigorous exercise on the day prior to the blood draw. Although this CPK elevation occurred at the end of the study, follow-up visits documented its resolution to below-baseline CPK level. The incidence of treatment-related myalgia was low and similar between the groups (1 on SIMVA 20 mg vs. 2 on EZE/SIMVA 10/20 mg). No cases of myopathy or rhabdomyolysis were observed with either treatment. There were no consecutive elevations in ALT or AST to ≥3 times the upper limit of normal, and no cases of hepatitis, jaundice or other clinical signs of liver dysfunction were reported during the treatment period. There were no deaths.

DISCUSSION

A recent pooled analysis of four factorial studies found that the coadministration of EZE with a statin (i.e., simvastatin, atorvastatin, lovastatin or pravastatin) may result in a lower incremental reduction in LDL-cholesterol levels in African Americans compared with Caucasians.[12] The explanation for this apparent difference was unclear, but the small sample size of African Americans (approximately 5% of the entire population) may have contributed to the finding. The present study was undertaken to better delineate the efficacy and safety of the coadministration of EZE/SIMVA 10/20 mg compared with SIMVA 20 mg in a large cohort of African Americans. After 12 weeks of treatment, coadministration of EZE/SIMVA 10/20 mg resulted in a significant incremental reduction in LDL-cholesterol levels (17.3%) compared with SIMVA 20-mg monotherapy. The enhanced efficacy of coadministration versus SIMVA monotherapy was consistently observed across various subgroups, including age, gender, baseline LDL-cholesterol level and other risk factors. Furthermore, the percent reduction in LDL-cholesterol level with EZE/SIMVA 10/20 mg enabled a significantly greater proportion of patients to reach their NCEP ATP III risk-specific LDL-cholesterol goal. EZE/SIMVA 10/20 mg also produced greater reductions in total cholesterol, triglycerides, non-HDL cholesterol and apo-B compared with SIMVA 20 mg. Changes in HDL cholesterol and hs-CRP were comparable between the treatment groups. The reduction in hs-CRP with SIMVA 20 mg in this study was comparable to that previously reported for SIMVA 20 mg.[14] In previous studies involving larger and broader populations, EZE has been clearly shown to produce significant incremental reductions in hs-CRP when coadministered with SIMVA.[14,15] It is unclear whether the failure to observe such an effect in the current study reflects a true finding or the absence of adequate statistical power to reliably address hs-CRP changes given the variability of this parameter.[16]

The reduction in LDL-cholesterol levels with SIMVA 20-mg monotherapy appeared to be lower in this cohort compared with the typical response observed in Caucasians. The results of the ARIES trial also suggested a blunted LDL-cholesterol response to rosuvastatin and atorvastatin in African Americans.[17] This reduced response was equivalent to approximately one statin dose halving in the ARIES study and in the present study. The reason for the apparent smaller statin response in African Americans versus Caucasians has not been elucidated. Nevertheless, the magnitude of the incremental LDL-cholesterol reduction (17.3%) observed between the coadministration of EZE/SIMVA 10/20 mg and SIMVA 20-mg monotherapy in the present study was consistent with that (15–16%) previously reported in predominantly Caucasian cohorts.[18,19]

The coadministration of EZE/SIMVA 10/20 mg was well tolerated in African Americans, with a safety profile similar to that of SIMVA 20-mg monotherapy. There appeared to be no increased risk of adverse events with EZE/SIMVA 10/20 mg. Only three patients discontinued for treatment-related adverse events (one in SIMVA 20 mg group and two in EZE/SIMVA 10/20 mg group). The three reported serious adverse events were not considered to be treatment related. There were no measured consecutive ALT/AST elevations ≥3 times the upper limit of normal in this study. One patient on SIMVA 20-mg monotherapy experienced an exercise-related CPK elevation to ≥10 times the upper limit of normal at the end of the study, which resolved at follow-up. No deaths or cases of myopathy or rhabdomyolysis were reported. Overall, these safety findings in African Americans are consistent with those found in other trials examining the coadministration of EZE and SIMVA in predominantly Caucasian populations.[9,18,19]

In summary, EZE/SIMVA 10/20 mg resulted in significantly greater improvements in atherogenic lipid profiles and was well tolerated compared to SIMVA 20-mg monotherapy in a large cohort of African Americans with primary hypercholesterolemia. Moreover, the incremental reduction in LDL-cholesterol levels with the coadministration of EZE/SIMVA 10/20 mg allowed more patients to reach their risk-specific NCEP ATP III LDL-cholesterol goal, and these results were similar to those reported in larger, predominantly Caucasian cohorts.

ACKNOWLEDGEMENTS

We thank Dr. Michael Davies for writing and editorial assistance with this manuscript. These data were presented in abstract form by Dr. Roxanne Rodney at the 2005 NMA national meeting in New York, NY.

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